LIN28 Binds Messenger RNAs at GGAGA Motifs and Regulates Splicing Factor Abundance.

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Public Summary:
One of the key genes important in stem cell self-renewal and pluripotency, and also used for reprogramming somatic cells into induced pluripotent stem cells is the RNA binding protein LIN28. To understand the roles of LIN28 in regulating the genes that are important in this process, we have performed biochemical experiments followed by sequencing to identify the RNA targets of LIN28. We find that LIN28 regulates other RNA binding proteins that regulate the splicing patterns of genes expressed in the cell, representing a new mode of regulation by this RNA binding protein, thought to only act through microRNAs.

Scientific Abstract:
LIN28 is a conserved RNA-binding protein implicated in pluripotency, reprogramming, and oncogenesis. It was previously shown to act primarily by blocking let-7 microRNA (miRNA) biogenesis, but here we elucidate distinct roles of LIN28 regulation via its direct messenger RNA (mRNA) targets. Through crosslinking and immunoprecipitation coupled with high-throughput sequencing (CLIP-seq) in human embryonic stem cells and somatic cells expressing exogenous LIN28, we have defined discrete LIN28-binding sites in a quarter of human transcripts. These sites revealed that LIN28 binds to GGAGA sequences enriched within loop structures in mRNAs, reminiscent of its interaction with let-7 miRNA precursors. Among LIN28 mRNA targets, we found evidence for LIN28 autoregulation and also direct but differing effects on the protein abundance of splicing regulators in somatic and pluripotent stem cells. Splicing-sensitive microarrays demonstrated that exogenous LIN28 expression causes widespread downstream alternative splicing changes. These findings identify important regulatory functions of LIN28 via direct mRNA interactions.

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